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NOVEL AMPHIPHILIC CHOLESTEROL-CONTAINING NANOCARRIERS FOR CREATION OF DRUG DELIVERY SYSTEMS

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Abstract. Nowadays, great achievements have been observed in the field of nanotechnology, especially in material science, supramolecular assemblies and drug delivery. In particular, the medical application of nanotechnologies, usually termed nanomedicine, has given a important push to the development of various types of drug-loaded nanocarriers, such as liposomes, nanoparticles, micelles etc. These systems able to serve as efficient diagnostic and/or therapeutic tools against heavy diseases, such as cancer, infectious or neurodegenerative disorders. Among the numerous classes of materials employed for drug delivery purposes, colloidal systems based on amphiphilic copolymers containing hydrophilic and hydrophobic segments have attracted much attention due to the possibility of synthesizing tunable chemical structures. Reversible addition fragmentation chain transfer (RAFT) polymerization is one of the most extensively studied controlled/living radical polymerization methods that can generate well-defined polymers with targeted molecular weights characteristics, compositions and controlled architectures. RAFT technique has been effective employed to develop complex molecular architectures, such as blocks, gradient and stars copolymers. (Co)polymers based on N-vinyl succinimide (VSI) cause intense interest due to possibility of application as hydrophilic nontoxic materials in medicine. Such copolymers can be easily modified by alkaline hydrolysis resulting in conversion of VSI units to the Nvinyl succinimidic acid (VSA) units. Currently, cholesterol, as an essential component of the plasma membrane, has been known to be involved in many cellular processes such as membrane property regulation, steroidogenesis, bile acid synthesis and cellular signal transduction.

In the present research a synthesis and investigation of novel promising nanocarriers based on amphiphilic copolymers with prolonged resistance to biodegradation was proposed. A series of novel gradient copolymers of N-vinyl succinimide and cholesterol (meth)acrylate were synthesized using RAFT polymerization. Copolymerization of monomers was conducted in THF under 70 °C using dibenzyl trithiocarbonate as chain transfer agent. The copolymers of VSI-co-ChMA and VSI-co-ChA with different content of cholesterol units were prepared using the variation of ratio of initial components in reaction mixture. To obtained the amphiphilic copolymers the alkaline hydrolysis of VSI units of VSI-co-Ch(M)A was carried out under mild conditions. The resulting copolymers consisted of N-vinylamido succinic acid (PVASA) moieties and cholesterol (metha)crylate segments. The synthesized copolymers were widely characterized using a set of physicochemical methods, namely gel-permeation chromatography NMR spectroscopy and TGA.

The preparation of nanoparticles from p(VASA-*co*-Ch(M)A) was performed *via* the phase inversion from organic solvent to water followed by lyophilization and final dispersion of probe in a buffer of choice. The self-assembled polymer particles were analyzed in regards of their size, zeta potential and morphology by DLS and scanning TEM methods. Moreover, the cytotoxicity of p(VASA-*co*-Ch(M)A) nanoparticles was evaluated by MTT-test.